197 Serum Chloride

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Definition

Chloride is an inorganic anionic halogen with an atomic weight of 35.5. It is distributed exclusively within the extracellular fluid compartment (ECF), which comprises the blood/plasma (or serum) compartment and the interstitial fluid compartment. Chloride is the major anion associated with sodium in the ECF (see Figure 197.1). Normal serum chloride concentrations range from 96 to 106 mEq/L.

Technique

Several techniques for the determination of chloride are available including (1) the autoanalyzer (a colorimetric technique—SMA and ACA methods); (2) a coulometric method; (3) a mercurimetric method; and (4) chloride-specific ion electrodes.

In the autoanalyzer method, chloride ions displace thiocyanate from mercuric thiocyanate. The free thiocyanate reacts with ferric ions to form a colored complex, ferric thiocyanate, which is measured photometrically.

$$Hg(SCN)_2 + 2Cl \rightleftarrows HgCl_2 + 2SCN^-$$
$$3SCN^- + Fe(NO_3)_3 \rightleftarrows Fe(SCN)_3 + 3NO_3^-$$
[$Fe(SCN)_3$ absorbs at 480 nm]

This technique is not specific for the chloride anion. Other halogens, including bromide and sulfhydryl ions, react with mercuric thiocyanate. Bromide has a *greater* affinity for the mercuric ion than chloride, so equimolar quantities of bromide yield more $Fe(SCN)_3$ than equimolar quantities of chloride. Therefore a small amount of bromide will result in a reaction that will be read as a marked elevation in the serum chloride determination.

The Cotlove coulometric chloride titrator is another technique that measures the total chloride concentration. With this method, the passage of a constant direct current between silver electrodes produces silver ions. The free silver ions react with the chloride forming silver chloride.

Direct Current

$$Ag \rightarrow Ag^+ \; Ag^+ + (Cl^-) \rightarrow AgCl$$

After all the chloride combines with Ag^+, free silver ions accumulate, causing an increase in current across the electrodes and indicating the end point to the reaction. Although various halogens have differing affinities for Ag^+, this method is insensitive to these differences, so 1 mEq of any halogen will result in the reaction being read as a 1 mEq rise in the serum chloride concentration. When the serum chloride determination by the autoanalyzer is out of proportion to the determination by the chloride titrator

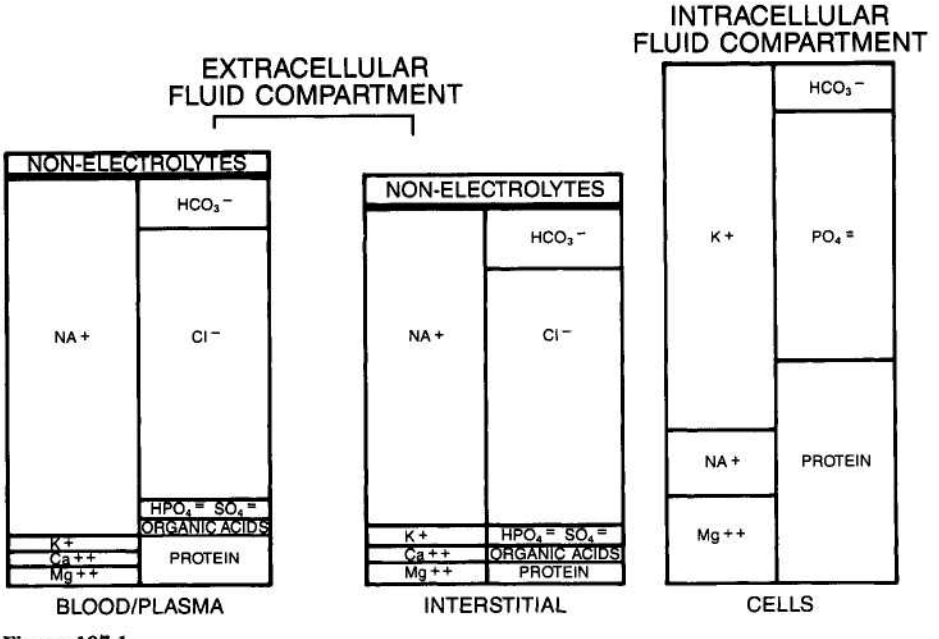

Figure 197.1
Electrolyte composition of body fluid compartments. The extracellular fluid compartment (ECF) is composed of the blood/plasma compartment and the interstitial fluid compartment. Chloride is confined to the ECF compartment.

technique, the presence of bromide is highly probable, and a serum bromide analysis should be performed.

In the mercurimetric method, chloride is titrated with a standard solution of mercuric ions and forms the soluble complex $HgCl_2$. The end point for the reaction is detected colorimetrically when excess Hg^{++} combines with an indicator dye, diphenylcarbazone, to form a blue color. Bromide will cause the same elevation of serum chloride as that which occurs during the coulometric titrator technique.

Chloride-specific electrodes are solid-state electrodes composed of membranes of AgCl. These electrodes can measure chloride potentiometrically in serum and in small quantities of sweat. Specific ion electrodes are presumably not susceptible to bromide or other halogen interference.

Basic Science

The kidneys are responsible for the maintenance of total body chloride balance. They maintain homeostasis because each kidney is composed of 1 million functional units, nephrons. Part or all of the chloride filtered by the initial portion of each nephron, the glomerulus, will be reabsorbed as a result of both active and passive transport processes along the tubules comprising each nephron. The ability of the nephrons to reabsorb chloride maintains the serum (and ECF) chloride concentration within a narrow range (Figure 197.2).

The majority of the filtered chloride is reabsorbed with sodium during transport through the first portion of the tubule, the proximal tubule. The reabsorption of chloride in this segment occurs in two phases. In the initial portion of the proximal tubule, sodium entry into the cell is linked to active co-transport of organic solutes (Na–glucose; Na–amino acids; Na–phosphate; and Na–organic anions) and to active secretion of H^+ from the tubule cells (and thus the reabsorption of HCO_3). Both of these active processes raise the intraluminal chloride concentration thus producing, in the later segments of the proximal tubule, the passive movement of chloride along a favorable concentration and electrochemical gradient (see Figure 197.2). In the straight portion of the proximal tubule, the pars recta, chloride reabsorption continues as a result of passive diffusion down a favorable electrochemical gradient.

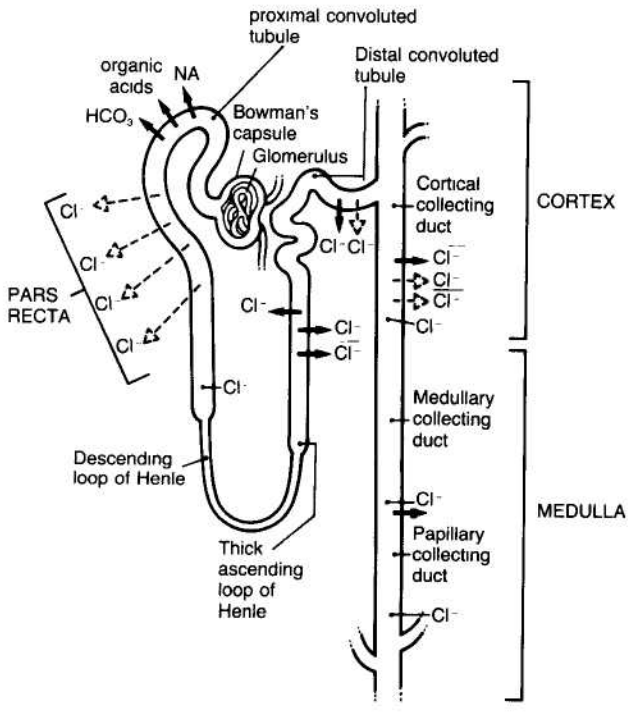

Figure 197.2
A typical nephron, the functional unit of the kidney. Each nephron is composed of a capillary bed for filtration, called the glomerulus, and tubule segments located in the cortex and medulla of the kidney. Chloride is both actively and passively transported in various segments of the tubules.

The descending limb of the loop of Henle, the next portion of the nephron, is relatively impermeable to NaCl, and no Na or Cl transport occurs. In the next segment, the thick ascending limb (loop of Henle), chloride is actively transported by a specific carrier-mediated process and Na^+ (or K^+) follows passively to maintain electroneutrality. The most recent data suggest a model in which two Cl^- ions are transported for each Na^+ and K^+. Evidence also suggests that chloride transport is further increased in this segment through the generation of cyclic adenosine monophosphate by antidiuretic hormone.

In the distal convoluted tubule, as in the proximal tubule, chloride transport may be passive or active. It has been postulated, but not proven, that chloride transport is coupled to energy provided by the passive influx of sodium into the cell. Other data suggest that the measured transepithelial potential difference is sufficiently negative to explain chloride movement down a favorable electrochemical gradient.

The last segment of the nephron, the collecting duct, is composed of three segments: the cortical collecting tubule, the medullary collecting tubule, and the papillary collecting tubule. Chloride transport occurs as a result of both active and passive processes in the cortical collecting duct, but by only active transport processes in the papillary collecting duct. No data are currently available for the medullary collecting duct.

In summary, both active and passive transport processes are important in the reabsorption of chloride by the nephrons of the kidney. The proximal tubule appears responsible for reabsorbing the majority of the filtered chloride, and the ascending loop of Henle reabsorbs another significant amount. The distal tubule and collecting duct, although reabsorbing a smaller quantity of chloride, may also play an important role in this balance. The quantity of chloride excreted into the urine (i.e., not reabsorbed by the tubules of the nephron) is not constant, but varies from day to day depending on whether the kidneys are trying to conserve or eliminate chloride. This ability of the kidneys to vary daily chloride excretion keeps total body chloride values relatively constant and maintains serum chloride concentrations within a narrow range despite marked daily variations in chloride intake.

The presence of specific clinical disorders can affect the ability of the kidneys to maintain chloride balance. The result is hyperchloremia (elevated serum chloride concentrations) or hypochloremia (reduced serum chloride concentrations.

Clinical Significance

The serum chloride value, like the serum sodium value, is a *concentration* measurement (e.g., the amount of chloride/

liter of plasma water). Therefore, the serum chloride concentration can be elevated above the normal range—hyperchloremia—either by the addition of excess chloride to the ECF compartment or by the loss of water from this compartment, and vice versa. The serum chloride concentration can be reduced below the normal range—hypochloremia—by the loss of chloride from the ECF or the addition of water to this compartment. This means that one cannot evaluate total body chloride stores from the serum chloride concentration. Clinical parameters must be used in conjunction with serum chloride values to assess the significance of hypochloremia or hyperchloremia.

Hypochloremia

Total body chloride depletion can result from both extrarenal and renal causes (see Table 197.1). Extrarenal causes include inadequate sodium chloride intake, losses of certain gastrointestinal fluids (e.g., vomiting and nasogastric suction associated with loss of HCl, or diarrhea as a result of abnormalities in small bowel transport), and loss of fluids through the skin occurring as a result of trauma (e.g., burns). Severe vomiting may lead to the most disproportionate loss of chloride compared to sodium since gastric chloride content is greater than 100 mEq/L and gastric sodium content is relatively low (20 to 30 mEq/L). In individuals with protracted vomiting or nasogastric suction, the serum sodium concentration may be only mildly depressed (130 mEq/L), whereas the serum chloride concentration is usually markedly lowered (80 to 90 mEq/L). The most reduced levels of serum chloride (range 45 to 70 mEq/L) are associated with pernicious forms of vomiting due to gastric outlet obstruction, protracted vomiting in alcoholics, or self-induced vomiting. Individuals with hypochloremia secondary to total body chloride depletion will have physical findings that indicate ECF volume contraction (e.g., hypotension, tachycardia, and orthostatic changes in blood pressure). Further support of total body chloride (and sodium) depletion is the finding of low concentrations of sodium and chloride in the urine. Renal causes of chloride (and sodium) losses include diuretic abuse, particularly loop diuretics; osmotic diuresis (e.g., mannitol, diabetic ketoacidosis, or hyperosmolar nonketotic coma); renal diseases associated with a salt-losing nephropathy including interstitial nephritis; chronic renal failure; postobstructive diuresis; and conditions associated with adrenal insufficiency (e.g., lack of endogeneous or exogeneous glucocorticoids or mineralocorticoids). The physical findings in individuals with hypochloremia as a result of renal losses of sodium and chloride will be similar to individuals with extrarenal chloride losses. In these individuals, however, the concentration of chloride and sodium in the urine will be elevated, indicating renal losses of chloride (and sodium) despite evidence of ECF volume contraction.

Table 197.1
Conditions Associated with Hypochloremia

Total body chloride depletion
Extrarenal
Inadequate NaCl intake
Losses of gastrointestinal fluids
Vomiting
Nasogastric suction
Small bowel fistulas
Burns
Renal
Diuretic abusers
Salt-losing nephropathy
Interstitial nephritis
Adrenal insufficiency
Dilutional (decreased chloride concentration)
Increased effective circulatory blood volume
Hypertonic infusions
Hyperglycemia (early stages)
Normal effective circulatory blood volume
Pathologic water drinkers
Intrinsic renal diseases
Hypothyroidism
Syndrome of inappropriate antidiuretic hormone (SIADH)
Drugs
Barbiturates
Chlorpropramide
Clofibrate
Morphine
Nicotine
Tricyclics
Decreased effective circulatory blood volume
Edema states
Congestive heart failure
Cirrhosis of the liver
Nephrotic syndrome
Acid–base abnormalities
Compensated respiratory acidosis
Metabolic alkalosis

Another finding often associated with total chloride depletion is metabolic alkalosis (blood pH greater than 7.45). The reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal and distal tubule is augmented because total body chloride depletion results in both ECF volume contraction (which stimulates HCO_3 reabsorption) and decreased quantities of filtered chloride available to the tubules for reabsorption with sodium. The virtual absence of chloride in the urine in the presence of a metabolic alkalosis is a strong indication that total body chloride depletion is present. Augmented reabsorption of $NaHCO_3$ will persist until adequate quantities of chloride are administered and/or the volume of the ECF compartment is normalized. Metabolic alkalosis also increases potassium excretion by the kidneys which can lead to hypokalemia.

A number of chloride-containing solutions can be used to correct total body chloride depletion including isotonic sodium chloride (normal saline, physiologic saline) for replacement of just sodium and chloride; potassium chloride for replacement of potassium and chloride; and lysine monochloride, arginine monochloride, ammonium chloride, or HCl when acid replacement is necessary in conditions associated with chloride depletion and severe metabolic alkalosis.

Clinical conditions associated with excess water retention can cause a dilutional hyponatremia with a proportionate decrease in the chloride concentration (see Table 197.1). This form of hypochloremia does not reflect total body chloride or sodium depletion, and, in fact, many of the conditions associated with dilutional hypochloremia have a normal or increased total body content of chloride and sodium. Individuals with dilutional hypochloremia generally have a normal or elevated blood pressure and evidence of ECF volume expansion. The sodium and chloride urine concentrations are variable depending on the underlying medical condition.

Specific acid–base abnormalities may also be associated with hypochloremia. Conditions associated with a respiratory acidosis (e.g., retention of CO_2 as with chronic obstruc-

tive lung disease) cause the proximal tubule to increase its secretion of hydrogen ion. This results in sodium being retained prefentially as sodium bicarbonate and not sodium chloride. Although this is a compensatory mechanism to help ameliorate the acidemia, the end result is increased concentrations of serum bicarbonate (greater than 30 mEq/L) and decreased serum chloride concentrations. Conditions causing dilutional hyponatremia and hypochloremia do not require chloride-containing fluids, since they do not have total body chloride depletion. However, respiratory acidosis associated with hypochloremia may need chloride-containing fluids if a metabolic alkalosis and/or hypokalemia is also present.

Hyperchloremia

Hyperchloremia is also associated with a variety of clinical conditions (see Table 197.2). Conditions causing an elevation of the serum chloride concentration and a concomitant elevation of the serum sodium concentration result primarily from disorders associated with loss of electrolyte-free fluids (pure water loss); hypotonic fluids (water deficit in excess of sodium and chloride deficits); or administration of NaCl-containing fluids. Loss of electrolyte-free fluids occurs in conditions with increased insensible losses as a result of increased sweating (e.g., fever); hypermetabolic states (thyrotoxicosis); increased ambient room temperature and inadequate water replacement (as a result of loss of thirst perception as seen in the elderly); in ill infants; and in individuals with altered mental status (stroke patients, postanesthesia, and narcotic medications). This results in hypotonic dehydration (e.g., loss of TBW and contraction of the ICF and ECF compartments) and an elevation in both the serum sodium and chloride concentration—hypernatremia and hyperchloremia. Loss of electrolyte-free fluids also occurs in clinical conditions associated with central or nephrogenic diabetes insipidus. Both conditions are associated with an inability to concentrate the urine and large volumes of dilute urine (urine osmolality less than plasma osmolality). However, hypernatremia and hyperchloremia will not develop in association with either of these latter abnormalities as long as individuals drink adequate amounts of fluid or are given adequate quantities of electrolyte-free intravenous fluids to replace the daily urine losses. Loss of hypotonic fluids occurs with certain types of diarrhea states and burns; in conditions associated with an osmotic diuresis (e.g., diabetic glycosuria, mannitol, glycerol); diuretics; following a postobstructive diuresis; and in association with some intrinsic renal diseases. Since more water is lost relative to sodium, the serum sodium chloride concentration rises. But since some sodium and chloride are excreted into the urine, the serum sodium and chloride concentrations will not be as elevated as that occurring in conditions associated with loss of electrolyte-free fluids. Administration of NaCl-containing fluids can also result in hypernatremia and hyperchloremia if excessive quantities of hypertonic solutions of sodium chloride (3 or 5%) are given iatrogenically in place of 5% D5/W or inadvertently administered during instillation in utero for a second semester abortion. It can also be found in association with saltwater drowning. Administration of hypertonic tube feedings without the concurrent administration of adequate quantities of free water to dilute the feedings to isotonicity can also cause hypernatremia and hyperchloremia.

Table 197.2
Conditions Associated with Hyperchloremia

Loss of electrolyte free fluids (pure water loss)
Skin losses
Fever
Hypermetabolic states
Increased ambient room temperature
Inadequate water intake
Loss of thirst perception
Renal losses
Central diabetes insipidus
Nephrogenic diabetes insiuidos
Loss of hypotonic fluids (water deficit in excess of sodium and chloride deficits)
Extrarenal
Diarrhea
Burns
Renal losses
Osmotic diuresis
Diuretics
Postobstructive diuresis
Intrinsic renal disease
Sodium gain
Administration of 3 to 5% NaCl
Saltwater drowning
Saline abortion
Hyperchloremic metabolic acidosis
Renal tubular acidosis
Interstitial renal disease
Multiple myeloma
Idiopathic
Drugs
Carbonic anhydrase inhibitors—acetazolamide
Topical sulfamylon acetate and metabolites
Small bowel diarrhea
Ureteral diversion procedures
Ureterosigmoidostomy
Ileal bladder
Ileal ureter
Administration of acidic salts
NH_4Cl
Arginine HCl
Lysine HCl
Hyperalimentation
Early renal failure
Primary hyperparathyroidism
Recovery from diabetic ketoacidosis
Respiratory alkalosis

Individuals with hyperchloremia secondary to electrolyte-free fluid losses will have physical findings of dehydration: dry mucous membranes, coated tongue, and no axillary sweat. Urine chloride and sodium concentrations may or may not be helpful. However, the finding of a dilute urine (Uosm less than 100 mOsm with low chloride and sodium concentrations) in the presence of hyperchloremia and hypernatremia most likely confirms the diagnosis of diabetes insipidus. With the loss of hypotonic fluids, individuals will have findings of both dehydration (a result of electrolyte-free fluid losses) and sodium depletion. As a consequence of the latter, such individuals will have evidence of ECF contraction (hypotension, tachycardia, orthostatic hypotension) in addition. In contrast, individuals with hyperchloremia secondary to administration of NaCl-containing solutions will have physical findings indicative of an expanded ECF volume: hypertension, edema, congestive heart failure, and pulmonary edema.

Elevated levels of serum chloride without increased levels of serum sodium occur as a result of clinical conditions that

predispose to a hyperchloremic metabolic acidosis. Individuals with this acid–base disturbance have a serum chloride concentration above 110 mEq/L (and a low bicarbonate concentration) in association with an acidemic blood pH (pH lower than 7.35). Hyperchloremic metabolic acidosis can occur when the kidney tubules (either proximal or distal) do not reabsorb adequate quantities of the bicarbonate filtered by the glomerulus. Disorders causing intrinsic damage to the tubules (e.g., interstitial nephritis); drugs that block bicarbonate reabsorption (e.g., carbonic anhydrase inhibitors—acetazolamide; and topically applied sulfur drugs and their metabolites used as a topical antibiotic in burn patients) result in the condition called renal tubular acidosis (RTA). A diagnosis of RTA can frequently be made if one finds a blood pH that is acidemic in association with a nonacidic urine (a urine pH above 5.5). Other causes of hyperchloremic metabolic acidosis include conditions associated with severe diarrhea having losses of bicarbonate equivalents (e.g., lactate and acetate); ureteral diversion procedures, which often have hyperreabsorption of chloride by the interposed bowel segment; and ingestion of acidic chloride-containing salts (NH_4Cl, arginine chloride, and lysine chloride); or acidic salts of amino acids found in some hyperalimentation solutions. Hyperchloremic metabolic acidosis can also be seen in the early stages of chronic renal failure, especially secondary to conditions resulting from interstitial renal damage; in the recovery phase of diabetic ketoacidosis (loss of ketone bodies in the urine prevents them from being converted to bicarbonate in the liver and results in bicarbonate deficits); and in primary hyperparathyroidism (which is associated with renal bicarbonate losses). In addition, respiratory alkalosis, a condition seen in individuals with hyperventilation (e.g., sepsis, pregnancy, pulmonary infections, anxiety) is associated with an elevated serum chloride concentration and a low bicarbonate concentration. An arterial blood pH will help distinguish between hyperchloremic metabolic acidosis and respiratory alkalosis.

Hyperchloremia is also seen with bromide intoxication because bromide is measured as a chloride equivalent by certain chloride measurement techniques. This results in the finding of an anion gap (as measured by the difference of sodium plus potassium minus chloride plus the total CO_2 content being less than 8 mEq/L). Although the use of medications with bromide has decreased, cases of bromide intoxications still occur. It is unusual to see acute bromide intoxication, since bromide causes significant gastrointestinal irritation, resulting in nausea and vomiting, making toxic levels difficult to achieve. Slow chronic ingestion of bromide, however, can lead to toxic levels, since bromide is excreted by the kidneys, and accumulation can occur if intake exceeds output. The clinical features of bromide intoxication include fever, neurologic disturbances, skin rash, and history of ingesting proprietary bromide-containing drugs. Toxic manifestations include irritability, delirium, sedation, psychic disturbances, tremors, motor incoordination, and increases in CSF pressure and protein. Spuriously increased levels of serum chloride concentration appear in bromism, but the degree of elevation is dependent on the chloride methodology employed. There may be a poor correlation between the severity of bromide intoxication and serum bromide levels. However, bromide intoxication will cause mental and neurologic symptoms when the serum levels of bromide exceed 9 mEq/L. Most patients show signs of bromide poisoning when the serum bromide concentrations are in the range of 19 to 25 mEq/L.

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